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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/282,879	03/31/1999	SUBROTO CHATTERJEE	46906-2-DIV	9227

21874 7590 03/10/2004

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/282,879	CHATTERJEE, SUBROTO	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Prosecution reopened

In view of the appeal brief filed on 12-4-03, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 13-17 and 31 are currently pending and are present for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 15-17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13, 15-17 are rejected because of the recitation of the phrase "or derivative thereof". While Examiner acknowledges that the specification defines

fragments or derivatives as proteins or polypeptides which retain the biological activity of sphingomyelinase (SM or N-SMase), the specification does not define what the metes and bounds of the term "derivative" are. That is to say, whether the derivative is any protein from any source with the same activity or must the protein have some amount of structural homology to SEQ ID NO:2? And if so how much homology must be present to be a derivative? Therefore, the claim as written does not convey the scope of "derivatives" encompassed rendering the claim unclear.

In their appeal brief, applicants have argued that the term is specifically defined at page 8, lines 15-24 of the application and that the extensive disclosure provided does not render the term indefinite. Examiner respectfully disagrees with such an argument. This is because the definition or explanation recited in the disclosure does provide the activity of the fragment and/or derivative, the question of its structural homology to SEQ ID NO:2 has been left unanswered. Until such time the claim as written does not convey the scope of "derivatives" encompassed rendering the claim unclear. Hence the above rejection is maintained.

Claims 13-17 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13-17 and 31 are drawn to a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, comprising contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO:2 or a fragment or a derivative of the same, followed by analyzing the mixture of the candidate agent

and the enzyme or the fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent. However, it is not clear to the Examiner as to which candidate agent is further selected as useful, i.e., the candidate compound which reduced the enzyme activity (an inhibitor/antagonist) or the candidate compound which in fact increased the enzyme activity (agonist). Furthermore while it is understandable that compounds which modulate the activity of an enzyme can be used for treatment of disorders involving said enzyme activity, it is not clear to the Examiner as to how such compounds can be used for diagnosis of a particular disorder involving enzyme activity.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-17, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder comprising contacting a pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO:2 and following the steps as recited in claim 13, does not reasonably provide enablement for such a method wherein a fragment or a derivative of the same, wherein said fragment of derivative has at least about 50% of the activity of SEQ ID NO:2 or wherein said fragment or derivative has an amino acid sequence that is at least 70% identical to SEQ ID NO:2 is used. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13, 15-17, and 31 are so broad as to encompass a method of identifying a compound useful in diagnosis or treatment of human sphingomyelinase disorder wherein said compound modulates the activity of the any sphingomyelinase including variants, mutants (derivatives) and recombinants or any sphingomyelinase having an amino acid sequence that is at least 70% identical to SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sphingomyelinases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single sphingomyelinase. It would require undue experimentation of the skilled artisan to make

and use the claimed polypeptides with said function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 as a sphingomyelinase but provides no guidance with regard to the making of variants, mutants, derivatives or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses all modifications and fragments of any sphingomyelinase (i.e., derivatives) or which encompasses all modification of sphingomyelinase with SEQ ID NO:2 (i.e., amino acid sequence with 70% identity to the enzyme of SEQ ID NOS:2) because the specification does not establish: (A) regions of the protein structure which may be modified without affecting sphingomyelinase

activity; (B) the general tolerance of sphingomyelinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including sphingomyelinases with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of sphingomyelinases required for the above method having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

As this is a newly instituted rejection, applicants have made no reference to the same in their appeal brief.

Claims 13 and 15-17, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 15-17, are directed to polypeptide derivatives corresponding to the sequence of SEQ ID NO:2. Claims 13 and 15-17 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, (modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of derived polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection applicants have traversed the above rejection arguing that the they cannot agree that the claims should recite only that enzyme and not other related N-

SMases. They submit that the specification discloses specific examples of acceptable N-SMases for the method. For example, applicants argue that enzyme fragments or derivatives that provide good activity in standard activity gel assays are discussed at page 8, lines 16-23 of the present application. However, a perusal of the specification at said page and line numbers does not actually reveal such information. Applicants also submit that the chemical structure of the native N-Smase is disclosed at both amino acid and nucleic acid levels and that important function domains in the structure recognized in pages 10-11. While it is agreed that the specification describes a sphingomyelinase with SEQ ID NO:2, there is no description of the structure of "derivatives" of the same. At times, it appears that applicants are arguing against a "enablement" rejection as opposed to the "written description" rejection under which said claims have been rejected. This is very obvious in the next set of arguments made by the applicants wherein they argue that those skilled in the art would be able to select appropriate N-SMases based on the assays and that those skilled in the art would reject derivatives that are inoperable. However, Examiner would like to remind applicants that above claims are rejected for lack of "written description" and would like to reiterate the following. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately

described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of "derivatives" in claims 13 and 15-17, includes species which are widely variant in structure. The genus of claims 13 and 15-17, is structurally diverse as it encompasses polypeptides with structural similarity to SEQ ID NO:2 as well as which lack any such similarity but are capable of N-SMase activity. As such, neither the description of the structure and function of SEQ ID NO:2 nor the disclosure solely of functional features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore the above rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561), Ogita et al. (WO 9518119, 7-6-1995)

and Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, 1987, pages 10.0.3-10.0.6). Claims 13-17 and 31 in this instant application are drawn to a method of identifying a compound which when used in a reaction comprising sphingomyelin as the substrate, the neutral sphingomyelinase as the enzyme and ceramide as the cleaved product, leads to reduced concentration of the cleavage product such that the identified compound could be used in the diagnosis or treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelin is treated with the enzyme sphingomyelinase under conditions wherein the substrate is cleaved and cleaved product, ceramide is detected (see page 12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the sphingomyelinase reaction was common knowledge in the art. However, while the above reference teaches a purified SM and an assay for its activity, it does not teach a recombinant SM or the use of recombinant SM in an assay for detection of a pharmacological agent even though the activity assay for the purified enzyme could be used for the same.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes,

leukemia, cachexia etc. Ogita et al. also teach an assay for determining the inhibitory activity of a compound using sphingomyelinase isolated from a rat brain wherein the assay is performed at a pH of 7.5 very close to the neutral pH. However, this reference also does not teach the use of recombinant SM.

Ausubel et al. in their voluminous manual teach all the techniques related to cloning a known protein starting from its purification stage up to obtaining its cDNA and the recombinant form of the protein. Examiner draws the attention of the applicant to the enclosed pages 10.0.3-10.0.6 wherein the reference teaches how one can obtain the oligonucleotide probe from a purified protein. Other chapters in the book also teach how one skilled in the art can make a specific cDNA library and use the oligonucleotide probe to clone the specific protein and obtain it in the recombinant form.

With the purified SM as taught by Chatterjee et al. and the knowledge existing in the art of protein biochemistry and molecular biology to make recombinant proteins and the importance of sphingomyelinase inhibitors as taught by Ogita et al., it would have been obvious to one skilled in the art at the time the invention was made to use the purified protein of Chatterjee et al., obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausubel et al. and use it to develop a method of identifying other compounds which inhibit sphingomyelinase on line with Ogita et al. such that compounds could become useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one of ordinary skill in the art would be motivated to do this in order to study the biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease and Ogita et al. teach that one of ordinary skill in the art would be motivated to do this

because, when the transmission of signals introduced by IL-1ß and TNF- α are blocked by inhibiting the activity of sphingomyelinase using an inhibitor, the symptoms of various diseases related to cytokines can be improved. One would have a reasonable expectation of success since Chatterjee et al. provide a purified sphingomyelinase and a robust and time tested assay method and Ogita et al. provide an assay and demonstrate the existence of a chemical compound which inhibits sphingomyelinase and Ausubel et al. provide time tested recombinant techniques that has been used by a number of other inventors.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Arguing against the above rejection in the appeal brief, applicant has traversed the above rejection that no *prima facie* case is presented by the cited documents, whether considered alone or in combination. Applicant also argues that the Office has not provided any prior protein or nucleic acid sequence and that knowledge of Ausubel's general cloning methods without more is not sufficient to render the claimed invention obvious. Applicant refers back to the Declarations filed by Dr. Chatterjee in which he has argued that the USPTO position was not tenable and that an antibody was required in order to isolate the cDNA clone.

Examiner respectfully disagrees with such arguments by the applicant and continues to maintain his position that there is no need for the Examiner to provide references which disclose amino acid or nucleic acid sequences to support the rejection as the art has advanced so much that the availability of purified protein is enough for one skilled in the art to identify the nucleic acid encoding such protein and obtain a recombinant protein. The procedures may be painstaking for some proteins, but still it can be achieved. Furthermore, even if the N-terminal

of the polypeptide is blocked and obtaining the amino acid sequence is difficult the art provides robust alternate methods which can be adapted in such cases to arrive at the cDNA clone. One such alternate method is the expression cloning method using λgt vectors and antibody developed using the purified protein as taught by Ausuble et al. Applicant has argued that it was the inventor who discovered that it was possible to make monospecific antibody against N-Smase which was required for cloning. While that may be so, the art teaches various methods to make monospecific antibodies against any given protein. Furthermore claims in question are not limited to those clones obtained by use of monospecific antibodies etc. and therefore, irrespective of the fact that the antibodies were needed for isolating the cDNA clone, said claims are rendered obvious by the reference of Chatterjee et al.

Finally applicant tries to point out the differences between the purified enzyme and recombinant enzyme to show a structure/function difference between the two. On this basis applicant argues that purified enzyme is tightly associated with proteases and phosphatases, less stable than recombinant enzyme, produces unwanted proteolytically digested products upon storage etc. However, none of these differences constitute a real structure/function difference between the purified enzyme and the recombinant enzyme. All said differences are consequential and does not merit consideration of the recombinant enzyme as unique from the natural purified enzyme. Therefore, contrary to all the arguments by the applicant against the rejection, Examiner continues to maintain his position that claims 13-17 and 31 are *prima facie* obvious over Chatterjee et al., Ogita et al. and Ausubel et al.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 6.30 a.m. to 3.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0939. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Manjunath N. Rao
Patent Examiner 1652

3-2-2004

Brenda Brumback
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